REMARKS

Claims 53, 56-58, 61-63, 65 and 66 are pending in this application. Claims 53 and 58 have been amended. Claims 55 and 60 have been canceled. Claims 65 and 66 have been added. Support for the language "400 mosmol/L" in claims 65 and 66 is found at least at page 10, line 12 of the specification. No new matter has been added. In view of the foregoing amendments and following remarks, Applicants believe that the rejections should be withdrawn and that all pending claims 53, 56-58, 61-63, 65 and 66 are in condition for allowance.

The undersigned representative of the Applicants appreciates the courtesies extended by the Examiner in a telephonic interview conducted on May 16, 2006. In the interview, the Examiner stated that he is open to allowing this patent application, even after the issuance of a Final Office Action. Also discussed in the interview were the recited dosage range amounts of the amino acids, in which the Examiner stated that he was looking for amendments to the claims in which the dosage amounts were reduced because the claimed dosage amounts are very close to the Hammond et al. disclosed dosage amount for arginine of 35.2 g. The Examiner also questioned whether osmolarity of the two amino acids of the present invention could be claimed.

35 U.S.C. § 103 Rejection

Claims 53, 55-58 and 60-63 stand rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,648,059 ("the '059 patent"), U.S. Patent No. 5,843,894 ("the '894 patent") and Hammond et al. (Br. J. Cancer, 1993;67:1437-1439). The Examiner states that the claims are rejected for the same reasons as has been made of record.

Applicants respectfully traverse this rejection and request that the rejection be reconsidered and withdrawn.

The claimed invention is directed to a method for inhibiting the renal uptake of proteins and peptides used for therapeutic or diagnostic purposes that possibly may be damaging to the kidneys of a subject, consisting essentially of administering a combination of lysine as a first amino acid, in which lysine is selected from the group consisting of D-lysine, L-lysine and poly-lysine, or a pharmaceutically acceptable salt or carboxylic acid derivative thereof; and a second amino acid selected from the group consisting of arginine and ornithine, or a pharmaceutically acceptable salt or carboxylic acid derivative thereof, wherein the first amino acid is administered in an amount of about 20-30 grams per treatment and the second amino acid is administered in an amount of about 20-30 grams per treatment.

The claimed invention also is directed to a therapeutic composition for inhibiting renal uptake of protein or peptides used for therapeutic or diagnostic purposes that possibly may be damaging to the kidneys of a subject, consisting essentially of one or more pharmaceutically acceptable excipients, carriers or diluents and a combination of lysine as a first amino acid, in which lysine is selected from the group consisting of D-lysine, L-lysine and poly-lysine, or a pharmaceutically acceptable salt or carboxylic acid derivative thereof; and a second amino acid which is selected from the group consisting of arginine and ornithine, or a pharmaceutically acceptable salt or carboxylic acid derivative thereof, wherein the first amino acid is provided in an amount of about 20-30 grams per treatment, and the second amino acid is provided in an amount of about 20-30 grams per treatment.

Applicants point out that lysine and arginine or ornithine therefore is present in a ratio of 0.67-1.5 in the method and composition of the present invention. Additionally,

the osmolarity of the combination of amino acids, as well as the therapeutic composition of the claimed invention is about 400 mosmol/L.

In contrast to the claimed invention, as previously made of record by Applicants, the '059 patent discloses administering an effective amount of a non-target reduction moiety, in which the preferred non-target reduction moiety is lysine and functional constituents or derivatives thereof. Although other moieties are disclosed as possible non-target reduction moieties, nowhere does the '059 patent teach co-administration of lysine with the other non-target reduction moieties. Furthermore, the disclosure of other non-target reduction moieties is provided in a list that happens to include "ornithine, arginine, epsilon amino caproic acid, cyclocaprone and the like." (Column 5, lines 18-19). More importantly, the '059 patent expressly states that "lysine is the preferred non-target reduction moiety for use in the present invention" (column 5, lines 20-21), and thus effectively teaches away from combining lysine with other amino acids generally, or arginine in particular. Applicants submit that such a general disclosure of a list of agents, one of which happens to be arginine, does not teach or suggest the co-administration of lysine and arginine in specific low dosage amounts of 20-30 g/l, which results in the new and unexpected synergistic effects of the claimed invention.

With respect to the '894 patent, as previously made of record by Applicants, this reference discloses a method of reducing kidney uptake of antibody fragment conjugates by solely administering lysine, either alone or as a mixture of at least two of D-lysine, poly-D-lysine or poly-L-lysine. Nowhere does the '894 patent teach or suggest the co-administration of specific low dosage amounts of 20-30 g/l of lysine and arginine. Furthermore, as discussed in the present application (on page 3, line 13 to page 4, line 3),

there are several disadvantages to administering lysine alone. In particular, Applicants have demonstrated that L-lysine administration in humans in an effective total dose of 75 grams can cause severe hyperkalemia, which may result in acute and life-threatening cardiotoxicity.

With respect to Hammond et al., Applicants point out that this reference does not disclose the co-administration of lysine and arginine. In fact, Hammond et al. disclose administering the amino acid preparation "Synthamin 14" without electrolytes, in which lysine and arginine are present. Hammond et al. expressly state, at page 1437, column 2, that "the amino acid preparation administered was Synthamin 14 without electrolytes, containing 4.93 g/l lysine and 17.6 g/l arginine and with a tonicity of 880 mosmol/l..." Synthamin 14 is a commercially available cocktail of fifteen amino acids which happens to contain lysine and arginine. As stated in the present application, at page 2, lines 18-22, amino acid cocktails such as Synthamin 14 typically comprise a total amount of about 100 grams or more of various amino acids which, in order to keep the osmolarity of such amino acid solutions safe for human infusion, the total volume of the infusion administered to a patient is in the range of 2 liters.

Thus, contrary to the Examiner's assertions previously made of record, Hammond et al. do not disclose administering 4.93 g/l lysine and 17.6 g/l arginine, but rather disclose administering 9.86 g/l of lysine and 35.2 g/l of arginine, along with 125.1 g/L of thirteen other amino acids. As stated above, amino acid preparations administered in such high amounts can cause severe hyperkalemia, which may result in acute and life-threatening cardiotoxicity.

Applicants therefore submit that one skilled in the art would not be motivated to practice the claimed invention based on Hammond et al. because this reference explicitly teaches that the beneficial effects of its amino acid preparation is due to the administration of lysine and arginine in a preparation in which thirteen other amino acids also are present. Furthermore, as Hammond et al. disclose, their amino acid preparation has an osmolarity of 880 mosmol/l, more than twice that typical of the claimed invention. Additionally, Applicants point out that, contrary to the lysine/arginine ratio of 0.67-1.5, which is the ratio of the two amino acids administered to a patient per treatment, as provided in the present invention, the ratio of lysine to arginine disclosed by Hammond et al. is 0.28, almost double.

In conclusion, Applicants respectfully submit that the '059 patent, the '894 patent, and Hammond et al., alone or in combination, neither teaches nor suggests the new and unexpected finding of the method and therapeutic composition of the claimed invention, namely, that the administration to a patient of a combination of two specific amino acids, e.g., lysine and arginine or ornithine, in amounts ranging from 20-30 g/L, results in a surprising synergistic effect when combined. Thus, lower doses of the two claimed amino acids can be given and still prove effective, which avoids serious side effects and inhibits renal uptake of protein and peptides which may be damaging to the kidneys. In other words, the dual low dose administration of lysine (or a derivative) and one of arginine or ornithine (or a derivative), and the unexpected results achievable thereby, are not taught or suggested by any or all of the prior art.

In view of the foregoing amendments and remarks, it is respectfully submitted that all pending claims 53, 56-58, 61-63, 65 and 66 in the present application are distinguishable from the cited prior art. Accordingly, reconsideration and withdrawal of the rejection and an early Notice of Allowance are respectfully requested.

Respectfully submitted,

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